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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	14

DATE MAILED: 06/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/614,326	EDELBERG ET AL.	
	Examiner	Art Unit	
	Thai-An N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27,29,30,32,33,43,45,52,53,57 and 69-86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27, 29, 30, 32, 33, 43, 45, 52, 53, 57, 69-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The request filed on 4/1/03 for a Request for Continued Examination (RCE) under 37 CFR 1.114 is acceptable and a RCE has been established. An action on the RCE follows.

Applicants' Amendment, filed 9/24/02, Paper No. 11, has been entered. Claims 26, 28, 48, 54, 56 and 58 have been cancelled. Claims 27, 29, 30, 32, 33, 43, 45, 52, 57, 69, 70, 72, 73 and 76 have been amended. Claims 78-86 have been added.

Claims 27, 29, 30, 32, 33, 43, 45, 52, 53, 57, 69-86 are currently pending and under examination.

Any rejection made of record in the prior Office action, mailed 3/25/02, Paper No. 9, and not made of record in the instant Office action, has been withdrawn in view of Applicants' arguments and/or amendments to the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27, 29, 30, 32, 33, 43, 45, 52, 53, 57, 70-75, 78-86 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of upregulating heart rate in a mammal by the direct myocardial injection

of a construct comprising at least one gene selected from the group consisting of: β_2AR, β_1AR, and $G_{\alpha s}$, the specification does not reasonably provide enablement for methods of upregulating heart rate in a mammal by the introduction of modified cells which are transfected with a gene selected from β_2AR, β_1AR, and $G_{\alpha s}$. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification teaches the transient transfection of cultured myocytes to assess genes that upregulate the heart rate. It was found that the percentage of myocytes with chronotropic rates greater than 60 bpm was higher in the β_2AR transfected myocytes as compared to the control cells. See Figure 1B and Example 1. The specification teaches that neonatal murine hearts were transplanted into the pinneas of adult mice and 4 to 6 weeks post-transplantation, the hearts were assayed for visual pulsation and electrocardiographic activity. After baseline ECGs were recorded, expression vectors containing the β_2AR genewere injected into the atrium of the transplanted hearts and electrocardiographic activity was recorded daily for up to 7 days following the injections. It was found that the injection of the transplanted hearts resulted in increased heart rate which was sustained for 3-4 days, after which, the heart rate returned to baseline levels. See Example 2, and particularly, p. 25, lines 9-19. The specification further teaches that 6 week old adult murine hearts were injected with expression vectors containing the β_2AR

gene. Electrocardiographic activity was recorded daily for 7 days following the injection. Increased heart rate was sustained for 2-3 days following the injection, after which time, the heart rate returned to baseline levels. See Example 3, and particularly, p. 27, lines 1-9. The specification teaches that Yorkshire pigs were injected into the right atrium with constructs encoding the human β_2AR gene. The heart rate of the injected animals was monitored for 3 hours, daily and 96 hours post-injection. It was observed that the heart rate of the pigs was increased for 1-2 post injection. See Example 4, and p. 31, lines 5-19.

The state of the art at the time of filing was such that it was unpredictable to transplant cells, of any type, for the breadth claimed, into the heart. For example, Alexander *et al.* [**Clinical & Experimental Pharmacology & Physiology** (1999) 26:661-668, cited in the Office Action mailed 5/10/01, Paper No. 6] state that with regard to cellular transplantation, cardiac myocytes were shown to fuse successfully with the host myocardium and were found viable for up to 4 months post-transplantation, but, "The transformed nature of the transplanted cells from these studies led to concerns over their unregulated growth potential. The grafts were not viable in the long term and there was no evidence for improved performance of the myocardium." Alexander further states that studies involving skeletal myoblasts also found long-term differentiated grafts but, "Again, there was evidence of tumorigenesis and no evidence for improved cardiac function." See p. 665, 2nd column.

The unpredictable state of the art of transplanting cells into cardiac tissue is supported by Strauer and Kornowski [**Circulation** (2003) 107:929-934] who state that, "Some major cell types, such as skeletal myoblasts, have the disadvantage of emboligenic potency when delivered systemically. Therefore, intramyocardial injection during open-heart surgery has been tested ... However, the therapeutic effect is limited because of severe arrhythomogenic complications." See p. 932, 1st column, 2nd full ¶. Murray *et al.* [**Journal of Cardiac Failure** (2002) 8:S532-S541] state that that fetal and neonatal cardiomyocytes that are introduced into the heart form a new myocardium, but the formation of the new myocardium is limited by graft cell death. Furthermore, they teach that skeletal myoblasts form larger grafts, but do not express gap junction proteins, and may not beat with host myocardium. They particularly state that, "One major challenge to myocardial repair is getting sufficient graft cell mass without risking a tumor-like overgrowth." See *Abstract.* For example, although cardiomyocytes can be grafted into injured hearts, their function is unclear, and there is often cardiomyocyte graft cell death, which limits the amount of new myocardium formed. See pp. S533-S535. Murray teach that although skeletal muscles and cardiac muscles placed in coculture formed a synchronously beating network, this coupling does not occur after *in vivo* after grafting. See p. S537, col. 1-2, bridging ¶.

Muller-Elmsen *et al.* [**Congest. Heart Fail.** (2002) 8:220-227] state that after cell transplantation into the heart, many cells have been able to survive and

integrate into the myocardium and improve function of diseased hearts, but the, "The current data suggest that whatever cell species is used, the best survival and integration may be accomplished if immature and undifferentiated cells are used." See *Abstract.* Muller-Elmsen further teach that the transplantation of somatic cells have problems such as immune response and graft survival, and that:

> *"[T]he requirements for successful transplantation of cardiac cells are more complex: not only must the donor cells be successfully grafted into the heart muscle, but they also must survive (at least a significant number of them) under adverse condition, with initial hypoxia and constant mechanical stress. In addition, to actively contribute to ventricular function, the transplanted cells must align with the host cells, and they need to electrically be coupled to the host myocardium. Thus, many questions need to be answered, including which disease can be treated, which cell type should be used as a graft, how many cells are optimal, and how should the cells be transplanted? Does this procedure improve cardiac function? Is there a direct contribution of grafted cells to contractility?"* See p. 220, 2nd column, last ¶.

Muller-Elmsen discuss various cell types that have been used in implantation research [see pp. 221-223], but clearly teach that the state of the art of cellular transplantation to cardiac tissue is unpredictable. For example, the cells used, the amount of cells, and the ultimate survival and engraftment of the transplanted cells. The claims read on any cell type; however, the specification fails to provide

guidance to show that any cell type, for the breadth claimed, would predictably upregulate heart rate, as the success of cellular transplantation is clearly dependent upon the type of cell used. Muller-Elmsen state that, "To date, many different cell types have been tested for transplantation into diseased hearts. Even though some comparative studies have been done, many questions remain unanswered, and the best cell type to use remains unknown." See p. 225, 1st column, *Summary & Conclusion.* They conclude that many studies have shown beneficial effects of transplanted cells in various types of heart disease, but, "[T]he mechanisms of these effects remain obscure and the impact of dosage [cell number] on the functional response is completely unclear. Therefore, there are many issues that need to be addressed before cellular cardiomyoplasty will eventually add to the therapeutic options for patients with heart disease." See p. 225, 2nd column, 1st ¶.

Thus, it is clear that the state of the art teaches that cellular transplantation into cardiac tissue is unpredictable. The specification fails to provide teachings or guidance as to the quantity of cells that would be required to provide a upregulation of heart rate. Furthermore, the claims as written, broadly read on any cell type. The above-cited art clearly shows that not all cell types would be able to engraft and function in the cardiac tissue, as the cells would be required to engraft properly, in sufficient numbers, function properly [*e.g.,* contract]. The specification fails to provide sufficient teachings, guidance or working examples to overcome the unpredictabilities associated with the *ex vivo* cardiac gene therapy.

Accordingly, in view of the quantity of experimentation required to overcome the unpredictabilities associated with cellular transplantation in cardiac therapy, the lack of teaching or guidance provided by the specification with regard to the transplantation of cells to upregulate the heart rate, the unpredictable state of the art of with regard to transplanting cells to cardiac tissue, as well as the breadth of the claims directed to the transplantation of any cell type, it would have required undue experimentation for one of skill in the art to make and/or use the claimed invention.

Claim 69 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for reasons of record advanced on pages 2-6 of the prior Office action. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claim is directed to a method of permanently upregulating heart rate in a mammal by introducing at least one fetal or embryonic cardiomyocyte transfected or transduced with at least one gene that upregulates heart rate, said gene selected from the group consisting of: β_2AR, β_1AR, and $G_{\alpha}s$.

The specification teaches the transient transfection of cultured myocytes to assess genes that upregulate the heart rate. It was found that the percentage of

myocytes with chronotropic rates greater than 60 bpm was higher in the β_2AR transfected myocytes as compared to the control cells. See Figure 1B and Example 1. The specification teaches that neonatal murine hearts were transplanted into the pinneas of adult mice and 4 to 6 weeks post-transplantation, the hearts were assayed for visual pulsation and electrocardiographic activity. After baseline ECGs were recorded, expression vectors containing the β_2AR genewere injected into the atrium of the transplanted hearts and electrocardiographic activity was recorded daily for up to 7 days following the injections. It was found that the injection of the transplanted hearts resulted in increased heart rate which was sustained for 3-4 days, after which, the heart rate returned to baseline levels. See Example 2, and particularly, p. 25, lines 9-19. The specification further teaches that 6 week old adult murine hearts were injected with expression vectors containing the β_2AR gene. Electrocardiographic activity was recorded daily for 7 days following the injection. Increased heart rate was sustained for 2-3 days following the injection, after which time, the heart rate returned to baseline levels. See Example 3, and particularly, p. 27, lines 1-9. The specification teaches that Yorkshire pigs were injected into the right atrium with constructs encoding the human β_2AR gene. The heart rate of the injected animals was monitored for 3 hours, daily and 96 hours post-injection. It was observed that the heart rate of the pigs was increased for 1-2 post injection. See Example 4, and p. 31, lines 5-19.

Although the specification provides sufficient guidance with regard to upregulating heart rate by the introduction of the constructs containing the β_2AR gene, the specification fails to provide teachings, guidance, or working examples with regard to *permanently* upregulating heart rate. The working examples provided by the specification clearly show that the observation of increase in heart rate is transient; for example, in the injected porcine hearts the heart rate was increased for 1-2 days post-infection. However, the specification fails to provide teachings or guidance as to permanent upregulation of heart rate.

Accordingly, in view of the quantity of experimentation necessary achieving permanent upregulation of heart rate by introduction in a mammal of at least one fetal or embryonic cardiomyocyte transfected or transduced with at least one gene that upregulated heart rate, the lack of direction or guidance provided by the specification for permanent upregulation of heart rate as claimed, it would have required undue experimentation for one skilled in the art to make and/or use the claimed pacemaker and methods of using the same.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The prior rejection of claims 76 and 77 is maintained under 35 U.S.C. 102(b) as being anticipated by Milano *et al.* [cited in the prior Office action].

The claims are directed to a cell in culture transduced or transfected with at least one gene that increases the rate of contraction of the cell, wherein the gene is selected from the group consisting of β_1AR gene, β_2AR and $G_{s\alpha}$ gene.

Milano *et al.* teach a construct containing the β_2AR that was used to create transgenic mice. They teach that in order to directly assess the effect of β_2AR overpression, atria were isolated from mice and placed in culture [see p. 584, 1st column, 1st full ¶ and p. 586, #21].

Milano anticipate the claimed invention because the increase in the rate of contraction of a cell transfected by the β_2AR gene is considered an inherent property of the gene. "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Accordingly, Milano *et al.* anticipate the claimed invention.

Claims 76 and 77 are rejected under 35 U.S.C. 102(a) as being anticipated by Drazner *et al.* [J. of Clin. Invest., 99:288-296 (1997), cited in the Office action mailed 5/10/01, Paper No. 6.

The claims are directed to a cell in culture transduced or transfected with at least one gene that increases the rate of contraction of the cell, wherein the gene is selected from the group consisting of β_1AR gene, β_2AR and $G_{s\alpha}$ gene.

Drazner *et al.* teach the transduction of cultured myoblasts by an adenovirus construct comprising the β_2AR gene linked at the 5' end to the CMV promoter and at the 3' end to bovine growth hormone poly A signal [bGH]. See p. 289, 3rd ¶, lines 1-8. They teach that the expression of the β_2AR gene increased camp [see Figure 4], indication potentiation of β adrenergic signaling.

Drazner *et al.* anticipate the claimed invention because the increasing of the rate of contraction of a cell transduced by a gene consisting of the β_1AR gene, β_2AR and $G_{s\alpha}$ gene is an inherent property of the gene. "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Accordingly, Drazner *et al.* anticipate the claimed invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thái-An N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to William Phillips, Patent Analyst, at (703) 305-3482. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

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